Attorney Docket No. 065691-0464

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Luc TERRAGNO et al.
Title:	METHOD FOR MAKING A LIQUID CONCENTRATE OF FOOD-GRADE ACCLIMATED AND VIABLE BACTERIA
Appl. No.:	10/590,658
International Filing Date:	2/28/2005
371(c) Date:	11/29/2006
Examiner:	Felicia C. King
Art Unit:	1789
Confirmation Number:	2153

AMENDMENT AND SUBMISSION ACCOMPANYING
A REQUEST FOR CONTINUED EXAMINATION

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This communication is responsive to the Final Office Action dated September 30, 2010, and is accompanied by (A) Exhibit A, (B) a Request for Continued Examination, and (C) a Petition for Extension of Time for three months, and the required fees, to make this response timely.

Amendments to the Claims begins on page 2 of this document.

Remarks/Arguments begin on page 6 of this document.

Please amend the application as follows:

Amendments to the Claims

Listing of Claims:

1. (Previously Presented) A production process for a liquid concentrate of adapted and viable bacteria, for use in foodstuffs comprising the following successive steps:

a) the bacteria are propagated in a fermenter in an appropriate culture medium;

b) the bacteria obtained in step a) are adapted;

c) the culture medium containing the bacteria adapted is washed by tangential microfiltration using a washing solution;

d) the washed medium containing the bacteria adapted is concentrated in bacteria by tangential microfiltration to a bacterial concentration greater than 5×10^{10} cfu/ml;

e) a liquid concentrate of adapted and viable bacteria for use in foodstuffs is recovered, and

wherein adaptation of the bacteria carried out at step b) is shown by measuring parameters of the culture medium and/or bacteria parameters, and wherein the bacteria are lactic acid bacteria.

2. (Canceled)

3. (Previously Presented) The process as claimed claim 1, wherein the culture medium of step a) is a synthetic medium.

4. (Previously Presented) The process as claimed in claim 1, wherein the culture medium containing the bacteria in the fermenter at the end of step a) has a pH between 3 and 6.

5. (Previously Presented) The process as claimed in claim 1, wherein the concentration of bacteria at the end of propagation step a) is greater than 2×10^{10} cfu/ml.

6. (Previously Presented) The process as claimed in Claim 1, wherein the parameters of the culture medium are the pH, the osmotic pressure, the temperature of the culture medium, or a combination thereof.

7. (Previously Presented) The process as claimed in Claim 6 wherein the parameter of the culture medium is the pH and in that the step b) is taken by reducing the pH by natural acidification.

8. (Previously Presented) The process as claimed in Claim 6, wherein the parameter of the culture medium is the temperature, and in that step b) is taken by reducing the temperature.

9. (Previously Presented) The process as claimed in claim 1, wherein the parameter of the bacteria is the size of the bacteria.

10. (Previously Presented) The process as claimed in Claim 1, wherein the distribution of the lengths of each bacterium is predominantly between 0.1 and 10 micrometres.

11. (Canceled)

12. (Previously Presented) The process as claim 1, wherein the tangential microfiltration membranes have a porosity between 0.01 and 0.5 μm.

13. (Previously Presented) The process as claimed in claim 1, wherein in step c) the inlet pressure of the culture medium in the microfiltration module is between 0 and 3 x 10^5 Pa.

14. (Previously Presented) The process as claimed in claim 1, wherein in steps c) and d) the rate of the permeate is between 0.001 and 0.1 $m^3/h/m^2$ of surface exchange.

15. (**Currently Amended**) The process as claimed in claim 1, wherein in step d) the transmembrane pressure is between 0.1 x 10^5 and 2 x 10^5 Pa ~~and advantageously between 0.1 x 10^5 and 0.5 x 10^5 Pa~~.

16. (Previously Presented) The process as claimed in claim 1, wherein in step d) the recirculation rate of the washed medium is between 0.5 and 3 $m^3/h/m^2$ of exchange surface.

17. (Previously Presented) The process as claimed in claim 1, further comprising prior to step a) successive steps of revival and preculture of the bacteria.

18. (Previously Presented) The process as claimed in claim 1, further comprising an additional step f), following step e), of packaging the liquid concentrate of adapted and viable bacteria in flexible and hermetic bags.

19. (Previously Presented) The process as claimed in Claim 18 further comprising an additional step g), following step f), of keeping the liquid concentrate of adapted and viable bacteria packaged in flexible bags and hermetic at a temperature between -50°C and +4°C.

20. (Previously Presented) The process as claimed in Claim 19, further comprising an additional step h), following step g), of reheating by adapted means of the liquid concentrate of adapted and viable bacteria packaged in flexible and hermetic bags.

21-27. (Canceled)

28. (Previously Presented) A production process as claimed in claim 1, further comprising the step of adding the liquid concentrate of adapted and viable bacteria to a food product at the end of a production line.

29. (Previously Presented) A production process as claimed in claim 28, wherein said liquid concentrate is added to the food product prior to packaging of the food product.

30. (Previously Presented) A production process as claimed in claim 1, wherein said bacterial concentration is greater than 1×10^{11} cfu/ml.

31. (Previously Presented) A production process as claimed in claim 1, wherein the bacteria are selected from Lactobacillus spp., Bifidobacterium spp., Streptococcus spp., and Lactococcus spp. genera.

32. (Previously Presented) The process as claimed in claim 10, wherein the distribution of the lengths of each bacterium is predominantly between 0.5 and 5 micrometres.

33. (Previously Presented) The process as claim 12, wherein the tangential microfiltration membranes have a porosity between 0.1 and 0.3 μm.

34. (Previously Presented) The process as claimed in claim 15, wherein in step d) the transmembrane pressure is between 0.1×10^5 and 0.5×10^5 Pa.

35. (Previously Presented) The process as claimed in claim 16, wherein in step d) the recirculation rate of the washed medium is between 0.8 and 1.25 $m^3/h/m^2$ of exchange surface.

36. (**New**) The process as claimed in claim 15, wherein in step d) the transmembrane pressure is between 0.1×10^5 and 0.5×10^5 Pa.

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claim 15 is amended, and the cancelled subject matter therefrom is now found in new claim 36. No new matter has been added, and no other changes to the claims are made. Accordingly, claims 2, 11, and 21-27 are cancelled, and claims 1, 3-10, 12-20, and 28-36 are pending.

II. Indefiniteness Rejection

The rejection of claim 15, for recitation of the phrase "advantageously between 0.1 x 10^5 and 0.5 x 10^5 Pa" is overcome by amendment.

III. Obviousness-type double patenting

The claims are provisionally rejected for obviousness-type double patenting (ODP) over application 10/590,507. Applicant respectfully traverses.

The ODP rejection is improper because the cited application 10/590,507 represents an unpatented set of claims that cannot properly establish a case of ODP. By virtue of its pendency, application 10/590,507 presents no basis for ODP, and would only properly evoke ODP upon allowance and issue. Simply put, one cannot have "double patenting" until a first patent exists. Accordingly, the ODP rejection is erroneous and should be withdrawn. Alternatively, Applicant requests holding in abeyance this rejection, pending indication of allowable subject matter.

IV. Non-Obviousness

The Office reasserts the previous rejections of the claims as allegedly obvious over Hayakawa et al., Journal of Fermentation and Bioengineering, 1990, vol. 70, no. 6, pp. 404-408 ("Hayakawa"), Maus et al., Journal of Applied Microbiology, 2003, 95, pp. 146-154 ("Maus"), for all references, and various additional references against specific claims.

Applicant cited to Reid et al., J. Appl. Bacteriol., 41: 321-324, 1974 ("Reid") and Crespo et al., Chemical Engineering Science, 47: 205-214, 1992 ("Crespo") for their teaching away from the use of tangential microfiltration ("TFF") for obtaining live cells. This teaching away is dismissed by the Office because the references "predate the prior art references used in the rejection" and that Hayakawa and Maus "clearly show that whatever concerns that were raised by Reid and Crespo have been either overcome in the art or were not relevant to give rise to questions of applicability within the art," to conclude that the invention "would have been obvious." Action at page 12.

Applicant respectfully disagrees for reasons of record, and in view of the following remarks and Exhibit A.

A. Hayakawa is prior to Crespo

The Office asserts that Applicant's references "predate the prior art references used in the rejection," and reasons therefore, that their teaching away has "been either overcome in the art or were not relevant." This assertion is *factually incorrect*. Hayakawa, teaching TFF, was published in 1990. Crespo, teaching away from TFF when cell viability is paramount, was published in 1992. Maus says nothing about TFF that would rebut Crespo's teaching, and therefore, based on this timeline, Crespo's teaching away rebuts Hayakawa, and is not addressed by Maus. Accordingly, the evidentiary value of Crespo remains.

B. The prior art does not solve the problem of cell viability after tangential filtration

Cell activity and viability after TFF is an essential feature of the invention, as previously noted. Despite long recognition of this problem, the art did not recognize Applicant's solution. A closer analysis of the art confirms that those of ordinary skill did not consider using TFF when bacterial viability was paramount.

Hayakawa used TFF to remove toxic metabolites (especially lactate), and thereby permit Lactobacillus casei to grow to a density greater than otherwise obtainable. The use of TFF to remove lactate is conceptually distinct from the use of TFF to concentrate cells. More

importantly Hayakawa focuses on dry cell weight and does not report on bacterial viability. The only number that reports CFU/ml appears to be a conversion from the dry weight, without any evidence that this conversion was accurate for cells that had been subjected to TFF.

Other art of record also fails to consider an impact on viability. For example, Carrère et al., J. Membrane Science, 186 (2001), 219-230, was concerned with obtaining lactic acid from the fermentation broth, not the bacteria. Ebner et al., USPN 3,974,068, is similarly concerned with obtaining a clear filtrate. While Reid (cited by Applicant) was interested in bacterial cells, these were *formalin treated* cells which were, by definition, already killed. Maus, the other key reference cited by the Examiner, says nothing about TFF, and does not teach that adaption can work for physical stressors, such as occur during TFF.

Therefore, the *only* reference of record that considers viability in the context of TFF is Crespo, who teaches that TFF causes extensive loss of viability and that "the accumulation of cytochrome c in the fermentation broth is an experimental testimony of cell rupture during cell recycle culture." In this context, not only is Crespo teaching away from using TFF, but supports Applicant's contention that Hayakawa is unconcerned with viability.

Accordingly, the assertion that the teaching away of Crespo "has been either overcome in the art or were not relevant" is completely unsupported by the facts.

As further evidence that, at the time of filing, the person of ordinary skill had not identified the present solution to the problem of viability following TFF, Applicant submits **Exhibit A**, being an English-language discussion from the Ph.D. thesis of Fernanda Steit[1], which was publicly presented on June 18, 2008, *i.e.*, more than 4 years after Applicant's priority date.

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[1]Fernanda STREIT, "INFLUENCE DES CONDITIONS DE RECOLTE ET DE CONCENTRATION SUR L'ETAT PHYSIOLOGIQUE ET LA CRYOTOLERANCE DE *LACTOBACILLUS DELBRUECKII* SUBSP. *BULGARICUS* CFL1," Doctoral Thesis in Microbial Genetics at the Paris Institute of Technology for Life, Food and Environmental Sciences (Agro Paris Tech), pp. 168-185, publicly presented on June 18, 2008. AgroParisTech is one of the Grande Écoles, *i.e.* at the top tier French academia.

Exhibit A notes that despite the known utility of TFF "[a]t present, no work is available about the use of cross-flow microfiltration for the concentration of lactic acid bacteria during starter production processes," (page 169) and proposing to determine if TFF would be appropriate for such a use. Pages 175-176, under "Effect of microfiltration conditions on the specific acidification activity of *Lb. bulgarius* CFL1" clearly describes therein a *"negative effect of microfiltration."* Accordingly, the drawbacks of TFF for concentrating bacteria that were set forth in Crespo et al. and Reid et al., remained valid concerns in 2008, and the presently claimed solution to this problem was not found in the prior art.

C. The present solution would not have been obvious

The Action concludes that:

> it would have been obvious to one of ordinary skill in the art to combine tangential flow with adapted bacteria since during the process of adapting bacteria; there is a decrease in cell populations [Maus, pg, 150, Results]. There is a need to cultivate and concentrate as many surviving cells as possible. Tangential flltration makes this possible because it provides a culture method that produces bacterial cells in high density [Hayakawa, pg. 404].

Action at page 12. This assertion is not only based on an erroneous factual analysis of the references, as discussed above, but constitutes legal error in applying impermissible hindsight to arrive at the present invention. Nowhere in the prior art it is proposed to combine bacterial adaptation and bacterial concentration by tangential filtration. *A fortiori* the prior art never contemplates bacterial adaptation as an appropriate preliminary treatment to subsequent bacterial concentration of a liquid medium, nor with any reasonable expectation of success.

Such a hypothetical "would have been obvious" argument stands in stark contrast to the clear teaching away found in Crespo, and Exhibit A's evidence that loss of viability following TFF remained a problem, in the view of the ordinary artisan, even after Applicant's filing date.

Thus, the rejection under 35 USC § 103 relies on errors of fact regarding the dates of various references, their relevance and teachings. Not only does the prior art teach away from the use of TFF where viability is essential, but this position is supported by post-filing evidence. The rejection also relies on errors of law, in using hindsight to reconstruct the present invention from the prior art, without any *a fortiori* reason found in the prior art, and despite a clear teaching away. Because the rejection relies on errors of fact and of law, withdrawal is believed proper.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. Examiner King is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By /Rouget F. Henschel/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4059
Facsimile: (202) 672-5399

Rouget F. Henschel
Attorney for Applicant
Registration No. 39,221